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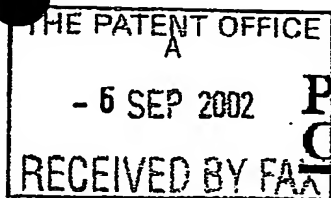
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Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

7021991003

4. Title of the invention

MICROFLUIDIC SYSTEM

5. Name of your agent (if you have one)

NOVAGRAAF PATENTS LIMITED

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Description

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Claim(s)

Abstract

Drawing(s)

8 only

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PETER WILSON (DR)

01904 610586

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MICROFLUIDIC SYSTEM

The invention relates to a microfluidic system having a modular construction for rapid assembly and disassembly.

5

Microfluidic devices and systems have become increasingly important in recent years for performing large numbers of different chemical and/or biological operations on a manageable scale, since they allow a large number of chemical or biochemical reactions to be carried out as part of an analytical and/or synthetic process in a relatively small liquid volume. Such miniaturised analytical or synthetic operations are generally more efficient, producing increased response times and reduce the requirement for potentially expensive reagents.

15 Conventional microfluidic devices and components have been constructed on a chip using technology analogous to that followed in the silicon fabrication industry in general, for example by constructing the devices in a planar fashion using photolithography and etching techniques. Conventionally, there has been a tendency, in particular by analogy with miniaturisation elsewhere in the silicon industry, to concentrate development efforts on miniaturising onto a single chip of as small a size as possible all chemical, biochemical and biological processing associated with a particular synthetic and/or analytical process.

25 Such constructions offer many advantages. However, the resultant chip is relatively inflexible. It is not always easy to intermix different materials and device technologies within such a single chip. Inspection, maintenance and repair can be complex.

It is an object of the invention to provide a microfluidic system which offers enhanced flexibility and which mitigates some or all of the disadvantages of single chip integral systems.

- 5 It is a particular object of the present invention to provide a modular microfluidic system in which various different microfluidic components are readily assemblable and disassemblable into a complete system to offer enhanced flexibility and utility.
- 10 Thus, according to the present invention in its in a first broadest embodiment there is provided a modular microfluidic system comprising at least one base board having a plurality of fluidly linked fluid supply apertures, preferably further having at least one fluid source aperture fluidly linked thereto, a plurality of microfluidic modules adapted to be detachably attached to the base
- 15 board, each having one or more fluid inlets and/or outlets, and a plurality of fluid couplings to effect releasable fluid connection between a module and a base board via a supply aperture on the base board and an inlet/outlet on the module.
- 20 In accordance with the invention, the microfluidic circuit is built up on the base board, with the "laboratory" system being formed in modular fashion upon the base board chip, rather than being integrated therewith in conventional manner. Fluid is supplied to the constructed microfluidic system via the fluid source aperture in the baseboard or by direct introduction into a
- 25 module. The base board chip is preferably constructed to provide a plurality of fluid channels and/or chambers linking in fluid communication at least some of the supply apertures to each other and/or to the source aperture. The fluid supply passages within the modules complete a desired microfluidic circuit when the modular structure is assembled.

The invention offers significant advantages, particularly in relation to flexibility of construction in use, when compared with prior art systems. Chip module to base board interconnections may be made conveniently compact and simple, whilst at the same time connections between the board and external equipment can utilise well established fittings for interfacing to that equipment. Intermixing of different materials and device technology is enabled (for example glass chips on a polymer board). In the same way a choice of external systems such as external pumps against on-board or module-surface mounted pumps and valves etc. is offered.

The system of the invention offers flexibility of design choice. For example a simple baseboard design may be provided with exchangeable complex modules, or complex systems may be included within the baseboard, with the modules attachable thereto being simple and/or disposable. Seals and connections between module and board can be selected according to module function.

The overall system provides for simple inspection and maintenance, flexibility of use, and ease of repair to systems, for example by replacing only a module which is defective rather than an entire system.

A microfluidic module in accordance with the invention comprises one or more microfluidic devices. As used herein, a microfluidic device may comprise any known element of a microfluidic system, including without limitation an active device unit, such as a reactor, heater, cooler, analyser, detector, mixer, processor or the like, a fluid function unit such as a pump, valve, filter or the like or merely a fluid channel and/or chamber to complete a particular microfluidic circuit.

Microfluidic devices in accordance with the invention may be three dimensional or generally planar. In a preferred embodiment, the devices are generally planar. Each module has a generally planar construction to be
5 incorporated upon a generally planar baseboard. Inlet/outlet apertures are most conveniently provided on one of the planar faces of such a module. Supply apertures are most conveniently provided on a planar face of the baseboard, and source aperture(s) may be provided at an edge or the same or opposite planar face thereof.

10

In particular, each module preferably has a generally planar sandwich construction, comprising at least one inner sandwich layer defining a fluid channel and/or chamber portion, and at least one cover layer covering and effecting enclosure of the same. In a preferred embodiment the module
15 comprises at least one sandwich layer defining an enclosed fluid channel and/or chamber portion, for example consisting of paired sandwich elements into the surface of at least one of which channels are created such that the pair assembled together define such an enclosure, with cover layers at either side thereof. Further intermediate layers may be present.

20

Active microfluidic elements may be incorporated within the channels and/or chambers so formed in the sandwich layer or additionally or alternatively may be provided upon the module surface in fluid communication with the channel therewithin. One or more inlet and/or outlet apertures are provided to effect a
25 fluid communication between the channel and an external surface of the module, for fluid connection to the baseboard. A baseboard may be similarly constructed.

Sandwich layers and cover layers are conveniently fabricated in suitable plastics material. Sandwich layers, which contact fluid in use, are preferably fabricated from chemically resistant plastics material, such as epoxy, SU8 epoxy being most preferred. This gives good resistance with good fabricability of fluid channels and chambers. Cover layers including fluid inlet/outlet ports might also contact fluid in use, and accordingly these are also fabricated from materials exhibiting good chemical resistance, for example epoxy or other plastics such as polyetheretherketone (PEEK).

Chemical properties of merely structural cover or intermediate layers might be less critical. However, any layers and in particular cover layers might also be modified for specific properties, for example for transparency, for electrical, magnetic or dielectric properties, to provide mountings for externally mounted microfluidic device components etc.

As used herein, microfluidic will be understood to refer to microstructures having at least some sub-millimetre dimensions, microstructure in this case being used to refer to any of a variety of well known structures in such systems, including, but not limited to, the channels and chambers hereinabove described, that are capable of providing passage or storage for a fluid.

In accordance with the invention, a plurality of fluid couplings are provided to effect a fluid-tight connection between at least one fluid supply aperture on a base board and at least one inlet/outlet on a microfluidic device module. Conveniently, this connection comprises a releasable coupling, for example in the form of a channel means removably insertable into a suitable recess in such a inlet/outlet/aperture to effect a fluid tight communicating connection therebetween. Such channel means conveniently comprises a tubular element, in particular a rigid tubular element, for example being parallel sided, for

example being square or rectangular, polygonal, or alternatively having a circular or elliptical cross section, with any recess into which such a tubular element is to be received preferably being shaped accordingly.

- 5 Such a tubular element can be a separable and distinct unit. However, for convenience, particularly in relation to the preferred embodiment where base board and module comprise generally planar components, the tubular element preferably comprises a projecting ferrule integral with and projecting from a first aperture comprising either a fluid supply aperture in the base board or an
10 inlet/outlet in the module, and adapted to be received in a recess comprised as a second aperture, correspondingly either an inlet/outlet in the module or a supply aperture in the base board. In particular the ferrule projects generally perpendicularly from a generally planar surface, to effect a fluid connection between a base board and module adapted to lie generally parallel when
15 connected.

In a most preferred form, ferrules are provided which project above the surface of the base board to be received within recesses comprising the inlet/outlet apertures of modules to be attached thereto.

20

Ferrules as above described can offer particular advantages. The ferrule system enables dead volume in fluid path between "chips" to be minimised. Use of ferrules allows higher density of interconnections than other fittings such as HPLC fittings and the like. Ferrules can withstand high pressures.

- 25 Ferrules generally require a reduced thickness of material in which to be held compared to the thickness needed to hold a screw thread or like fitting, allowing much thinner layers, down to layers essentially comprising films, to be interconnected. One or a few mechanical fasteners can be used to hold together a system making multiple fluid connections through the ferrules.

The ferrules ensure accurate mechanical alignment of fluid elements making accurate module placement easy.

- 5 It is generally easy to machine suitable ferrule recesses within the materials typically envisaged for use for baseboard and modules, giving scope for a range of ferrule and recess shapes. The internal bore and external diameter can be varied within limits, making it possible for the ferrule to incorporate microfluidic functionality. For example the internal bore could incorporate a
- 10 filtration function, optionally comprising multiple holes (in manner analogous to a photonic crystal). For example the ferrule can be modified to a larger shape to include a reservoir function.

- 15 Optionally the ferrule can incorporate additional functionality. It may contain a non-return valve, for example a ball valve. The ball valve could conveniently be magnetically switchable valve. The ferrule could contain a catalyst frit or could incorporate a filter. Various switches could be conceived.

- 20 It is possible to use a conducting for example metallic ferrule for electrical interconnection between chips. Such a metallic ferrule may optionally be provided with an insulating layer on a fluid and/or module contacting surface, effecting an electrical contact between modules and/or electrical contact with fluid therein. A ferrule based design offers particular flexibility in that the system may readily be provided with further functional interconnections (eg
- 25 magnetic, optical) either integral with or separately from the ferrule.

Optionally the ferrule can incorporate or be provided with a closure for closing a pathway not being used in a particular device combination allowing redundancy in pathway choice in base board for example during plug and play

use. The closure may comprise a bung to be applied by a user, or an integral closure valve adapted to be operated manually, or to operate automatically on insertion of ferrule into recess.

5 The invention hereinabove has been described in terms of a single baseboard with a plurality of modules disposed in a single layer thereupon. It will be readily appreciated that the invention is not so limited. A particular flexibility of the invention is that it allows for multi-level stacking of modules and/or base boards and/or intermediate level boards. Such intermediate level boards
10 may serve merely to provide fluid connections in the form of channels, chambers or the like, or may also include active microfluidic components. Similarly, it will be understood that the invention encompasses modular structures comprising a plurality of modules as hereinbefore described and at least one base board, in which the base board is also optionally provided with
15 active microfluidic components.

Intermediate level boards may be constructed as above described and preferred features thereof will be construed by analogy. In particular, boards are preferably planar, and preferably of a sandwich construction as above.

20 In embodiments comprising such a multi-level stacking system, any component adapted for use at an intermediate level will comprise at least one inlet aperture on a first "lower" surface and at least one outlet aperture on a second "upper" surface (it being understood that lower and upper are being
25 used herein as a convenience to refer to surfaces proximal and distal to the base board, and not to imply any restrictive orientation). References herein to inlets/outlets in a module will be understood to apply equally where appropriate to such a lower aperture, and references herein to a base board fluid supply aperture will be understood to apply equally where appropriate to

such an upper aperture in an intermediate level component. It is particularly easy to stack multiple layers using the preferred ferrule embodiment.

5 In a preferred embodiment, fluid connections are effected by projecting ferrules between components adapted to lie generally parallel. In multi-level systems, it will be convenient that these ferrules all project in the same direction. In particular, ferrules are preferably provided at apertures in the upper surface of the base board and at apertures in the upper surface of all intermediate level modules, to be receiving engaged in fluid tight connection
10 within recessed portions at apertures on the lower surface of all intermediate level components and all top level components.

Attachment of a module to the board, or of an upper layer module, to a lower layer module in multi-layer systems, may be achieved by any suitable
15 releasable attachment means, including without limitation screws or screw fixings, bayonet fittings whether quick release or not, push and snap fit connectors, vacuum or mechanical clamping connections, releasable mutually engageable resilient hook and felt pads, hooks, clips etc. The fluid couplings themselves, especially in the preferred form as channel means in interference
20 fit between pairs of linked apertures, for example ferrules engaged in interference fit in recesses, may assist in or even suffice to constitute such mechanical connection. However, additional mechanical connectors will usually be preferred.

25 The system in accordance with the invention provides a plurality of interchangeable elements enabling a plurality of different microfluidic functions to be performed, on one or more levels.

The invention will now be described by way of example only with reference to Figures 1 to 8 of the accompanying drawings wherein:

Figure 1 illustrates in cross section how fluid connection is effected between components in accordance with the invention;

- 5 Figure 2 is a schematic illustration of the basic construction of a microfluidic device for use with the invention;

Figure 3 is an example microreactor system employing the principles of the invention;

Figure 4 is a plan view of the baseboard of the reactor of Figure 3;

- 10 Figure 5 is an on chip manifold from the reactor of Figure 3;

Figure 6 is a plan view of a first active microfluidic device from the reactor of Figure 3;

Figure 7 is a plan view of a second active microfluidic device from the reactor of Figure 3;

- 15 Figure 8 is plan view of a third active microfluidic device from the reactor of Figure 3.

Figure 1 illustrates in cross section the basic design of fluid connection in accordance with the preferred embodiment of the invention employing projecting ferrules.

20

Illustrated schematically in Figure 1 are a baseboard (1), a first level component layer (2) and a second level component layer (3). The three layers are shown in exploded view disassembled but aligned for assembly.

25

Fluid connection within the system is effected by insertion of ferrules (7, 9) respectively provided at an upper supply aperture in the base board (1) and at an upper outlet aperture in the first level board (2) which are received in the recesses (6, 8) respectively provided in a lower surface of the first level board

(2) and in a lower surface of the second level board (3). In the embodiment, the connection employs simple parallel-sided holes to take PTFE tubes forming the ferrules (7, 9) although it will be understood that more complex holes and ferrules are possible. The ferrules are retained within the holes in
5 interference fit to provide a fluid tight leak proof connection.

In the example shown fluid supply is effected via an inlet fluid source aperture (10) comprising flexible tubing (11) of 1/16 inch (1.5 mm) diameter retained within HPLC fittings (12). The fluid path is shown by the dark line (14).

10

To assemble the modular structure into a laboratory system, a mechanical load is applied in the direction of the arrows (L) to effect engagement between the ferrules (7, 9) and the recesses (6, 8). Additional mechanical fixings (not shown) might be provided to ensure a more secure mechanical connection
15 between the components (1, 2, 3).

A simple schematic device construction is illustrated in the exploded view in Figure 2. The example device has a sandwich layer structure comprising an external base layer (21) of polyetheretherketone (PEEK), a pair of inner layers
20 (22) of SU8 epoxy and an upper layer (24) of polymethylmethacrylate (PMMA) and internal layers (22). Channel means (23) are provided in the inner epoxy sandwich layer (22) to provide the necessary microfluidic microstructure. Fluid ports (24) through the upper layer (24) give a fluid communication from a surface of the completed device to the channel means
25 (23) which form enclosed internal channels once the two parts illustrated in the exploded view of Figure 2 are assembled.

The sandwich layer elements (22) and upper layer (24) contact fluid in use, respectively in the channels (23) and ports (25). Accordingly these are

fabricated from materials exhibiting good chemical resistance, in the example respectively SU8-epoxy and PEEK. Properties of the merely structural lower layer (21) are less critical.

5 The simple schematic in Figure 2 does not illustrate any active microfluidic devices. It will be understood that these could be incorporated suitably within the channels themselves (for example in particular if these take the form of pumps, valves, filters or the like) or could be incorporated on a module surface in fluid communication with the channels (23).

10

A microfluidic reaction system in accordance with the invention is illustrated in plan view in Figure 3. The reactor comprises inlets for two supply fluids ("fluid A" and "fluid B"), and provides for three processing streams ("stream 1", "stream 2", "stream 3").

15

The reactor comprises a baseboard (31) incorporating a plurality of fluid supply channels (32) therewithin. The base board has a number of microfluidic components mounted thereupon, being a manifold (34) to split the supply fluid (A, B) into the three streams (streams 1, 2, 3), and then within
20 each stream a series of modules comprising a mixer chip (35), a detector chip (36), a reactor chip (37) and a further detector chip (36). These components are shown separately in Figures 4 to 8.

A system constructed in accordance with the principles of the invention as
25 illustrated by figure 3 offers admirable simplicity and flexibility, providing a number of advantages over conventional designs. In particular it enables use of larger interconnect components and scaling from the macro to the micro world by microfluidic "fanning" (transition from large pitch to small pitch spacing between fluidic channels). Fittings from chip to board enable close

packing of interconnections on <2 mm square packed spacing or <1 mm staggered spacing.

Figure 4 illustrates in plan view the baseboard (31) of Figure 3 without the components attached. The fluid channel means provided within the baseboard (32) are illustrated more clearly.

The manifold (34) of Figure 3 is illustrated in greater detail in plan view in Figure 5. It can be seen from Figure 5 how the manifold receives from a single inlet the two fluids (fluid A, fluid B) and produces 6 outlets, 1 to 6, effecting a paired supply of fluid A and fluid B to the three streams illustrated in Figure 3.

The device is constructed in accordance with the principles of Figure 2. Channel size in the example is $150\text{ }\mu\text{m}$ by $50\text{ }\mu\text{m}$. Routing is effected through 300 micron channels. The overall size of the device is 62 by 72 by 4 mm.

Figure 6 illustrates in side view (above) and plan view (below) the micro mixer chip of Figure 3. The micromixer chip receives two fluid streams comprising fluid A and fluid B respectively in inlet A and inlet B. These are mixed together as they follow the flow channel (41) to the outlet. The chip is of a basic design as illustrated in Figure 2, with a channel size of $100\text{ }\mu\text{m}$ by 50 microns and an overall size of 45 by 25 by 4 μm . It is retained in position on the baseboard by means of the clamp (42).

Figure 7 is a representation of a reactor chip (37) from Figure 3 shown in side view (above) and plan view (below). Fluid flows from inlet to outlet via the flow channel (51) thereby passing through the reactor portion (53). The reactor portion comprises a catalyst bed (54) 3 mm in diameter and 2 mm deep

retained by the screw in plug (55). The overall assembly has a channel size of 100 μm by 50 μm , an overall size of 36 by 25 by 6 mm, and is retained in position by the clamp (52).

- 5 Figure 8 illustrates the detector chip (36) of Figure 3 in side view (above) and plan view (below). Fluid flows from inlet to outlet via the flow channel (61). The detector's active area (68) includes a light source in the form of an LED (63) or an optical fibre (not shown) to an external source, a diffraction grating (64) and a light collector in the form of the optical fibre (65). A lens (66) in front of the light source collimates the light and a lens (67) in front of the light
10 collecting fibre improves the light collection efficiency. Collected light is sent for spectral analysis.

- Additional electrical detection function is provided via groups of 3 gold
15 microelectrodes (69), 110 μm wide on 200 μm pitch. Channel size is 400 μm by 400 μm , giving an overall device dimension of 50 x 30 x 5 mm.

Detail of de-mountable interface

Figure 1

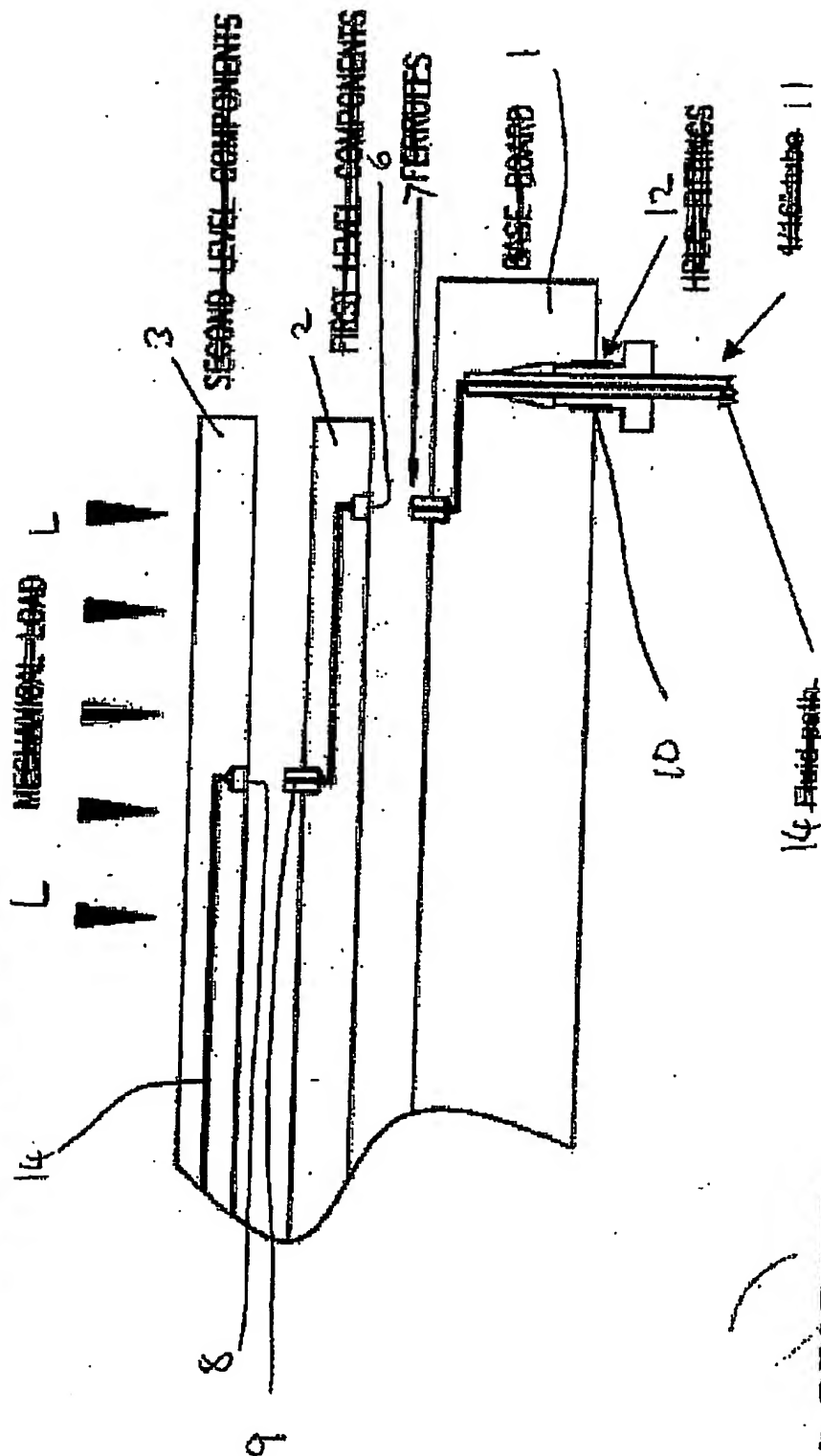
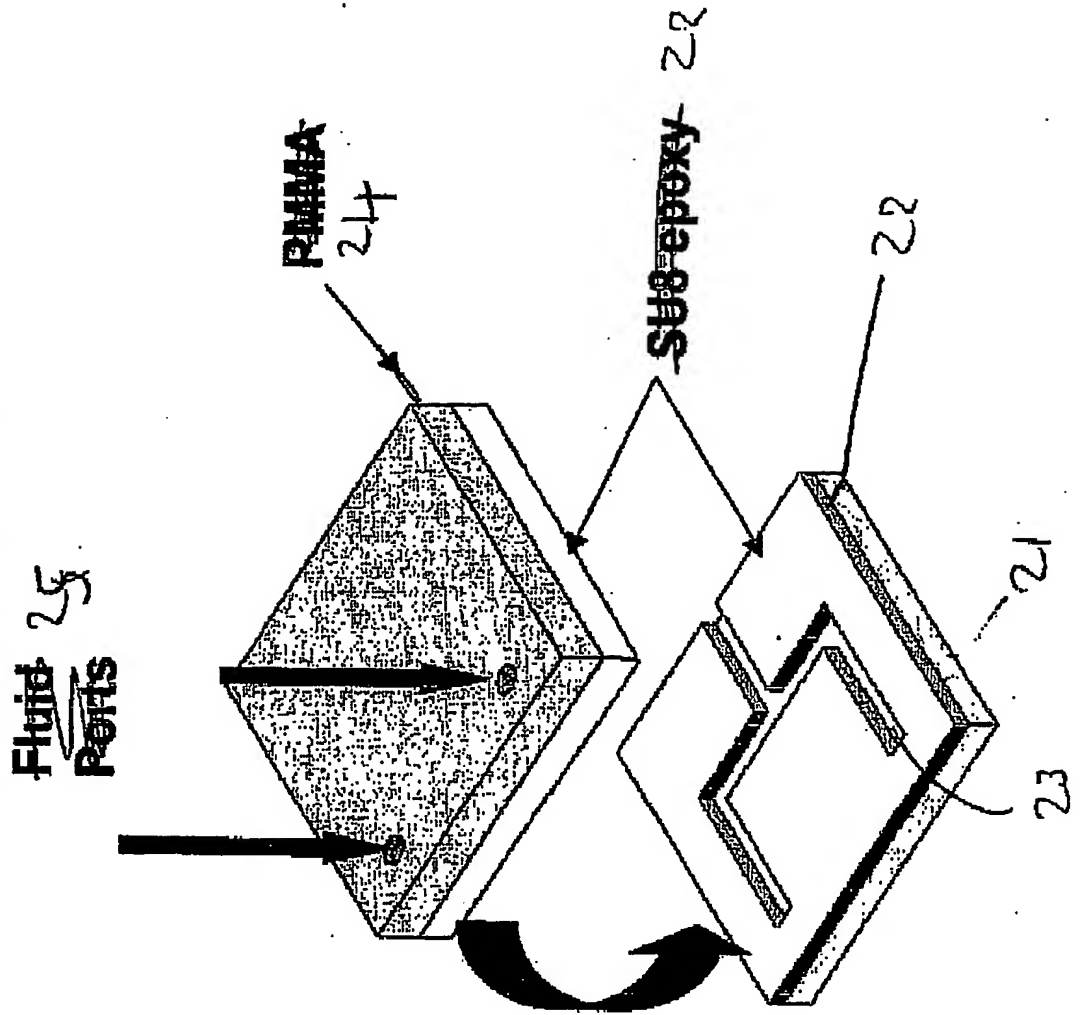


Figure 2

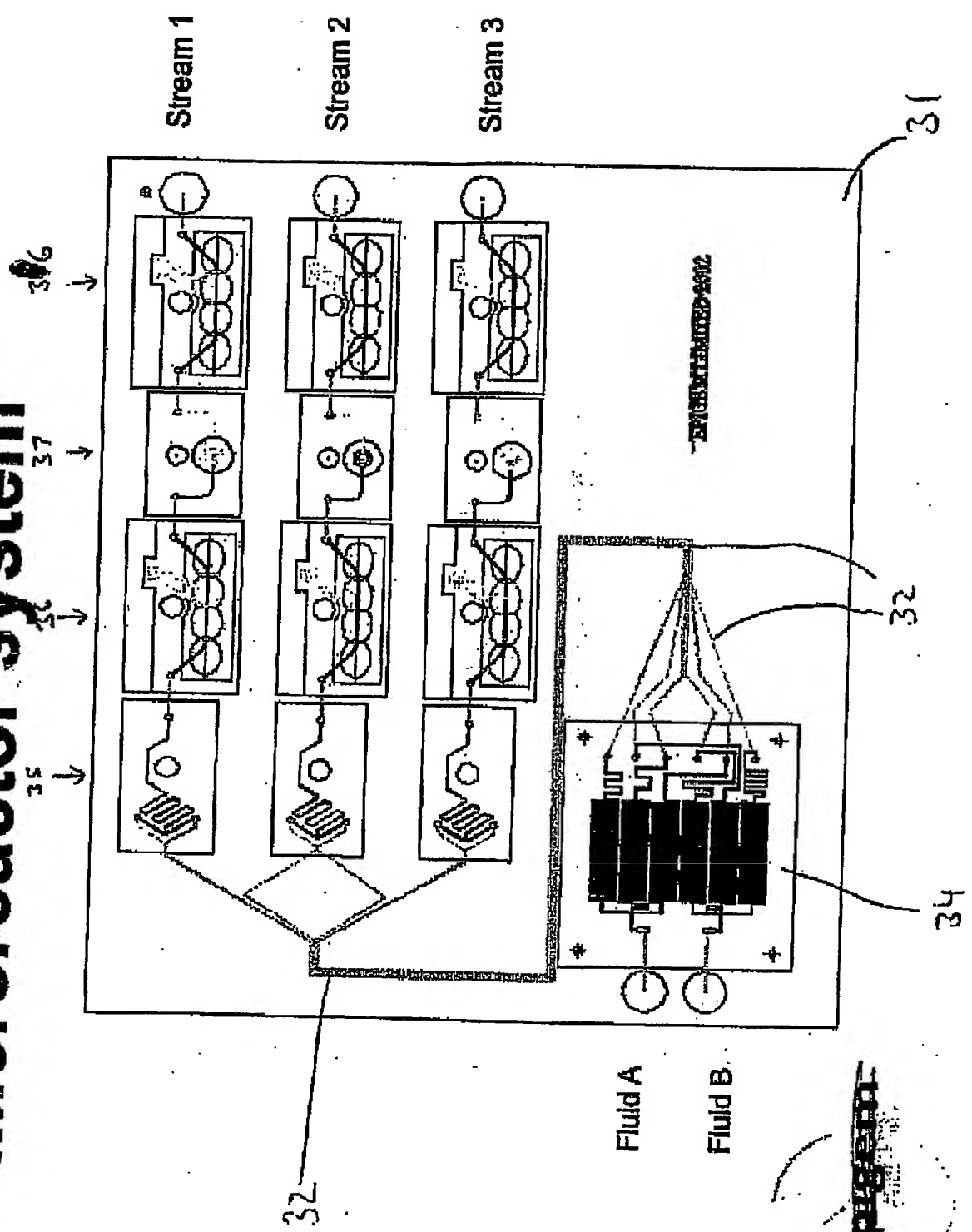
Device construction



epigem

Figure 3

Microreactor system



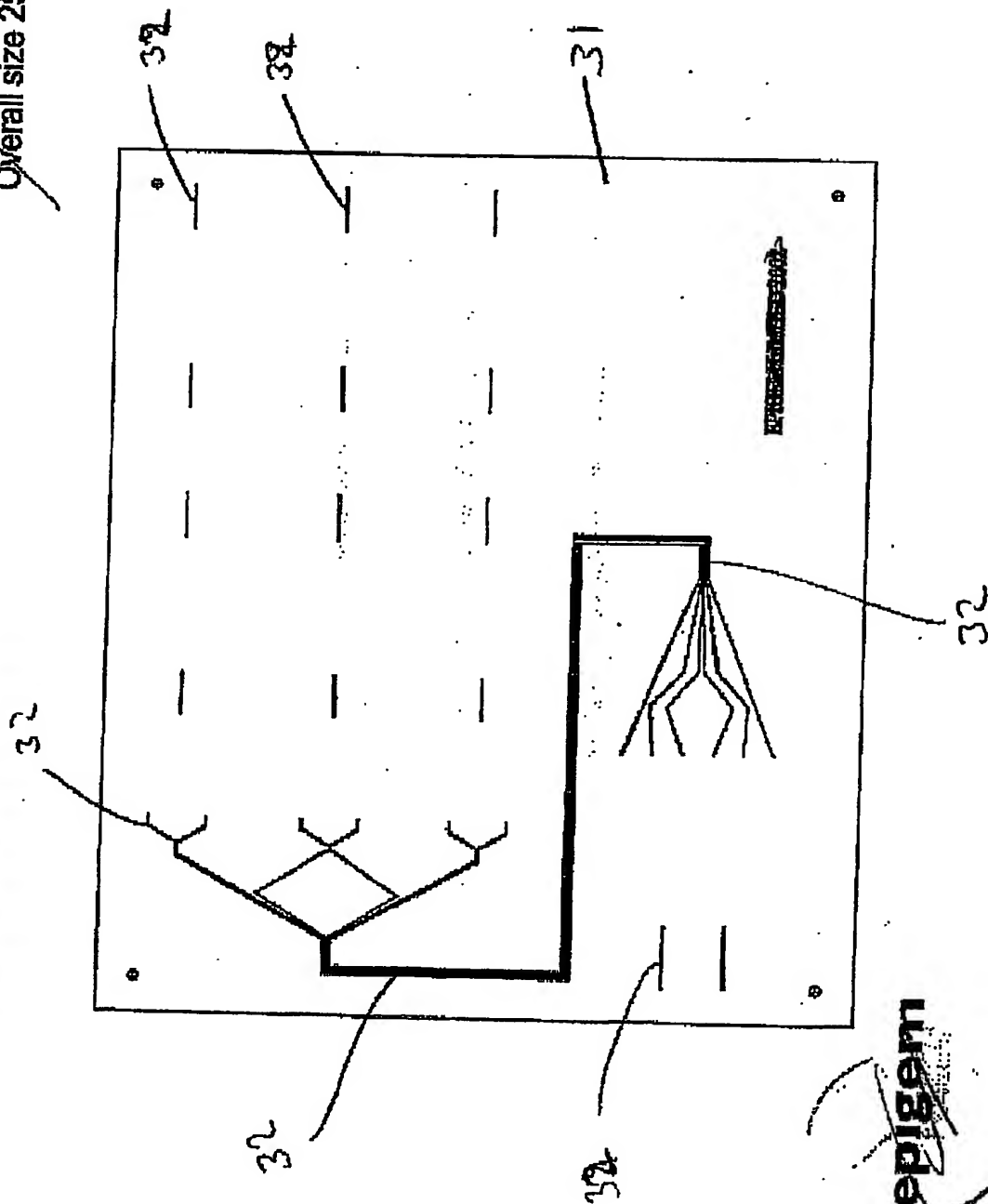
Baseboard

Figure 4

Design

Channel size 200 μm x 50 μm

Overall size 250 x 200 x 6 mm



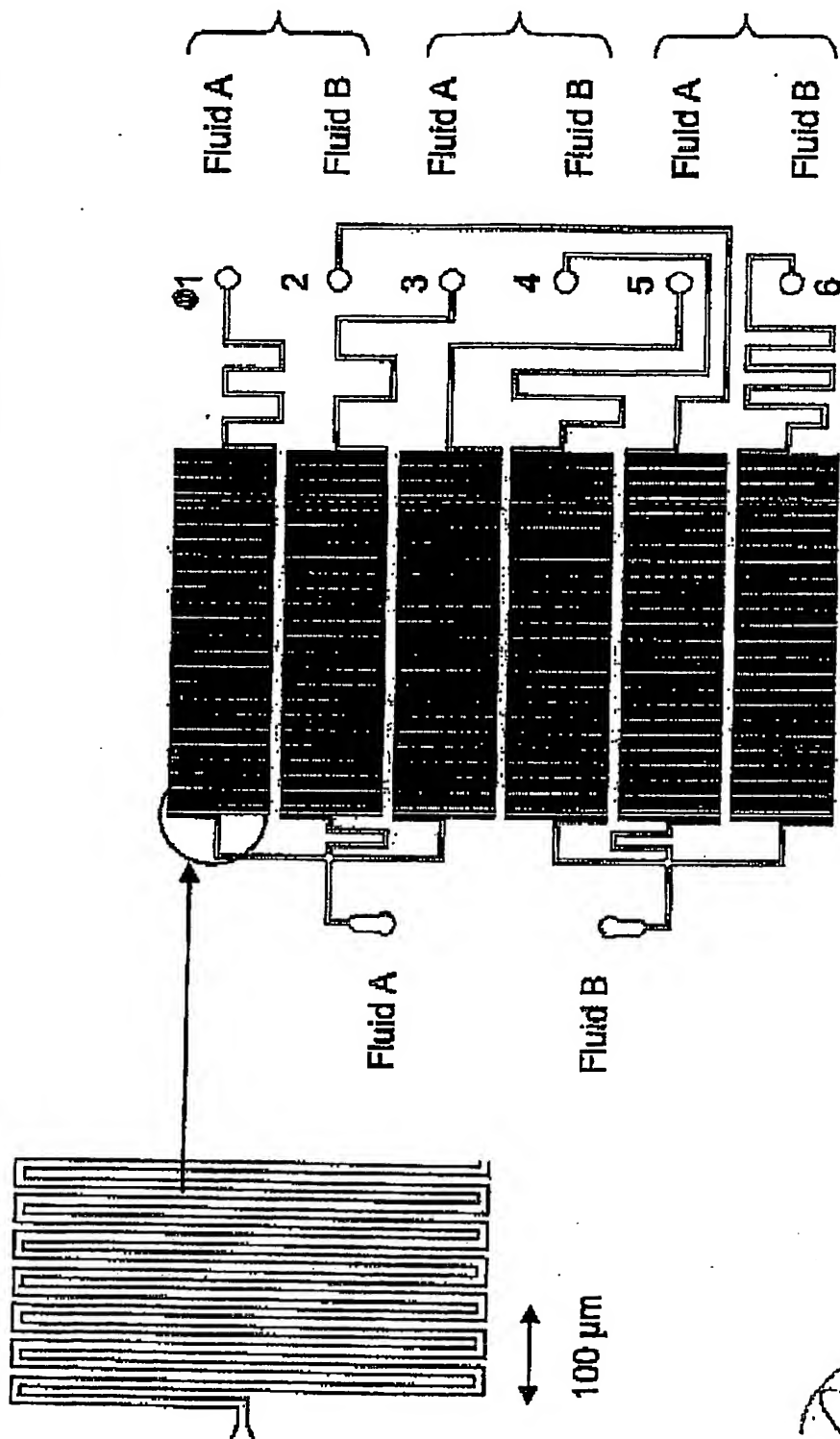
epigem

Figure 5

On-chip manifold

Design

Channel size 150 μm x 50 μm
 Routing with 300 μm channels
 Overall size 82 x 72 x 4 mm



34

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Micromixer chip

Figure 6

Design

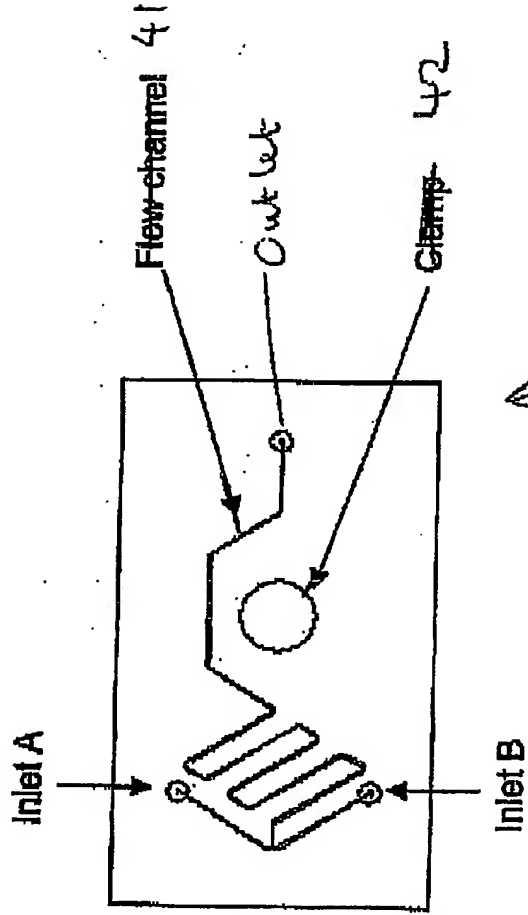
Channel size 100 μm x 50 μm

Overall size 45 x 25 x 4 mm

Side view



Plan view



35

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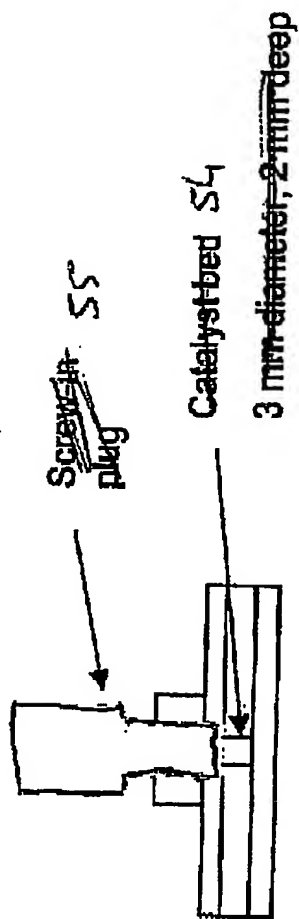
Reactor chip

Figure 7

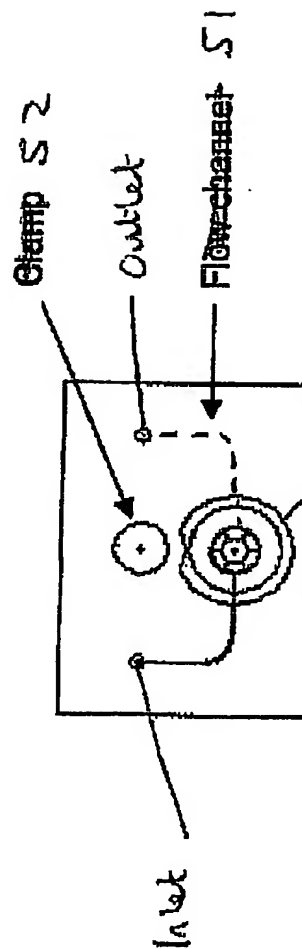
Design

Channel size 100 μm x 50 μm

Overall size 36 x 25 x 6 mm



Side view



Plan view

epigen

37

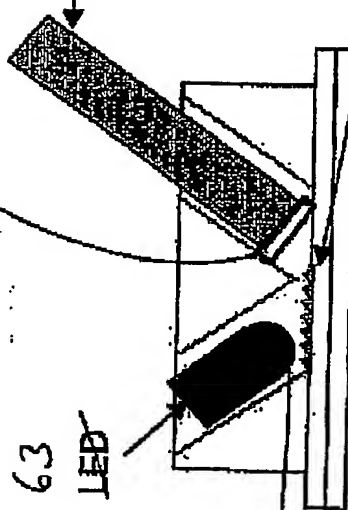
Detector chip

Figure 8

Design

Channel size 400 μm x 400 μm
Overall 50 x 38 x 5 mm

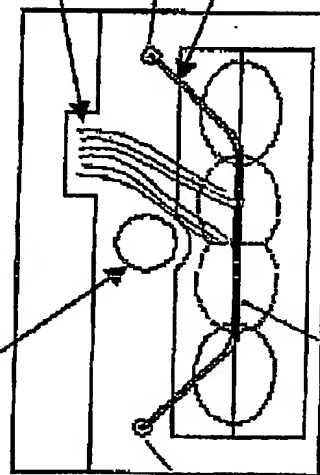
Optical fibre 65



Side view

Diffraction Grating 64

Clamp 62



Plan view

Groups of 3 gold microelectrodes 69

100 μm wide on 200 μm pitch

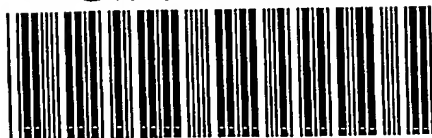
Outlet

Flow channel 61

Inlet

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PCT Application
GB0303853



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